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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/851,058 | Applicant(s) PARKER ET AL. | |
|---|---|---|---|
| | Examiner Lisa V. Cook | Art Unit 1641 | |

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Amendment Entry*

1. Applicant's response to the Office Action mailed 7/28/03 is acknowledged. In amendment-B filed therein the specification along with claims 1, 8, 13, and 21 have been modified.

2. Claims 1-22 are pending and currently under consideration.

## NEW GROUNDS OF REJECTION

### *Specification*

3. The amendment filed 10/30/03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C.132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicants have amended the abstract to read on two or more "structurally identical" and differentially isotopically labeled protein reagents while the disclosure teaches "chemically identical" and differentially isotopically labeled protein reagents. See claim 1 step (b). Chemically identical does not necessitate that the labels are structural identical. For example see page 12 lines 12-14, page 14 lines 15-18, and page 19 lines 8-16. Also the abstract recites the use of two or more sets of said labeled proteins (claim 1 step (c) while the disclosure only teaches the use of a single labeled protein set. In other words the instant claims read on at least four labels (two sets) while the specification only teaches two labels (one set). For example see page 8 lines 5-8, page 16 lines 4-5, page 22 lines 5-12, page 27 – Example 1 and page 30 - Example 3 wherein 2 labels are employed (d0ICAT and d8ICAT), and page 27 – Example 2 (utilizes 2 labels biotinyl iodoacetamide and non-deuterated reagent).

Therefore the amendment to the abstract is new matter. Applicant is invited to show support for the amendment. Applicant is required to cancel the new matter in the reply to this Office Action.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, claim 1 is drawn to a method employing two or more "structurally identical" and differentially isotopically labeled protein reagents while the disclosure teaches "chemically identical" and differentially isotopically labeled protein reagents. See claim 1 step (b). Chemically identical does not necessitate that the labels are structural identical. For example see page 12 lines 12-14, page 14 lines 15-18, and page 19 lines 8-16. Also the abstract recites the use of two or more sets of said labeled proteins (claim 1 step (c) while the disclosure only teaches the use of a single labeled protein set. In other words the instant claims read on at least four labels (two sets) while the specification only teaches two labels (one set). For example see page 8 lines 5-8, page 16 lines 4-5, page 22 lines 5-12, page 27 – Example 1 and page 30 - Example 3 wherein 2 labels are employed (d0ICAT and d8ICAT), and page 27 – Example 2 (utilizes 2 labels biotinyl iodoacetamide and non-deuterated reagent). Applicant is invited to show support for the newly claimed subject matter.

*Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 is vague and indefinite because it is not clear as to how the set of two or more structurally identical and differentially isotopically labeled protein reagents in 1(b) will be utilized when two different or differentially labeled proteins will react with the protein in step (a). In other words it is not clear if the labeling reagents provided in step (b) interact with the sample or not. Appropriate correction is required.

B. Claim 1 step (a) provides a set of labeling reagents (one for each sample) but does not recite that the labels bind the two different samples. This becomes more unclear in step (c) because it appears to recite additional labels, which do not have a specifically recited purpose with respect to the sample. For example it is not clear from the claims that the labels actually bind the proteins in the samples or are merely present in the sample mix. Accordingly appropriate correction is required.

C. Claim 1 step (c) recites the limitation "set of protein sample" in step a. However step (a) of claim 1 does not recite a "set of protein sample". There is insufficient antecedent basis for this limitation in the claim.

D. In claim 1 step d it is not clear if either of the two different samples is included in the mixture. As recited the all the labels are mixed to generate a single solution. It is suggested that the claims include the sample or read on the combination of mixtures (b) and (c).

E. Claims 1 and 13 remain vague and indefinite because the claims are drawn to a method reacting each protein sample with a different reagent of a reagent set. See claim 1 step (c) for example. This is ambiguous because it is not clear if the proteins are reacted with both reagents of the set or only one label. Please clarify.

## *Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1-3, 6-9, and 10-21 are rejected 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807).

Aebersold et al. teach methods of analyzing proteins or protein function in complex mixtures. The method utilizes labeling compositions comprising the formula A-L-PRG. Wherein A represents an affinity label, PRG is a protein reactive group, and L is a linker group. This same formula is taught in the instant disclosure on page 8. The PRG selectively reacts with certain groups that are typically found in peptides (sulfhydryl, amino, carboxy, homoserine lactone groups). One or more affinity labeled reagents with different PRG groups is introduced into a mixture containing proteins. After protein A-L-PRG mixing the digestion is optional. The PRG complex binds with the proteins of interest to produce a measurable tagged binding entity. This entity can subsequently be evaluated/analyzed via liquid chromatography/mass spectrometry (LC/MS). See abstract and page 8.

The method can be employed to screen and identify proteins, which are differential expressed in cells, tissue, or biological fluids. It is further possible to determine the absolute amount of the proteins utilizing known amounts of internal standards. See page 9 1st paragraph. The process is applicable in determining the state of protein modification, enzyme activity, and function. See pages 9-11.

Aebersold et al. differ from the instant invention in not specifically including a protein separation step involving electrophoresis (claim 1 step (e)), transblotting and digestion (claim 9) in their protein identification method.

However, Bienvenut et al. disclose methods of combining transblotting (OSDT), gel digestion of all proteins in parallel (PIGD) applied to electrophoresis techniques to increase the throughput of protein identification and characterization in proteome studies. The procedures included 1-DE and 2-DE gel electrophoresis. See page 4804. Peptides liberated during transblotting of proteins through an immobilized trypsin membrane were trapped on a PVDF membrane and identified by mass spectrometry. See abstract and pages 4801-4803.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the OSDT, PIG, electrophoresis combination procedure of Bienvenut et al. in the protein identification method of Aebersold et al. because Bienvenut et al. taught that the combination "led to greatly improved digestion of high molecular weight and basic proteins without loss of low molecular weight polypeptides. See abstract.

One of ordinary skill in the art would have been motivated to employ the combination procedure of Bienvenut et al. to take advantage of an automated integrated system involving MALDI-TOF MS scanning, spectra treatment, protein identification, in order to generate a fully annotated 2-DE map for protein identification. See page 4807.

II. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) and in further view of Yates et al. (US Patent #5,538,897).

Please see Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) as set forth above.

Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) differ from the instant invention in not specifically teaching protein/peptide sequence via tandem mass spectrometry.

However, Yates et al. disclose a method of correlating a peptide fragment with amino acid sequences derived from a database. A peptide is analyzed by a tandem mass spectrometer to yield a peptide fragment mass spectrum (mass fingerprinting). A protein sequence database or a nucleotide sequence database is used to predict/identify the fragment. For each candidate sequence, a plurality (pool) of fragments of the sequences is identified and the masses-m/z ratios of the fragments are predicted and used to form a predicted mass spectrum. See abstract.

Aebersold et al. in view of Bienvenut et al. and Yates et al. are all analogous art because they are from the same field of endeavor; all three inventions teach methods involving protein fragment characterization and identification.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize tandem mass spectrometry database sequence comparison as taught by Yates et al. to identify the fragments found in the method of Aebersold et al. in view of Bienvenut et al. to evaluate a pool of modified protein sequences, because Yates et al. taught that the patented system for correlating fragment spectra with known sequences would avoid delay and/or subjectivity in hypothesizing or deducing candidate amino acid sequences from the fragment spectra. (Column 1 lines 44-62).

One having ordinary skill in the art would have been motivated to do this because in order to achieve maximal data processing/protein manipulation to determine the parameter of interest.

III. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) and in further view of Clauser et al. (Proceedings of the National Academy of Sciences, USA, 1995, 92(11), 5072-6).

See Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) as set forth above.

Aebersold et al. in view of Bienvenut et al. differ from the instant invention in not specifically teaching post-translational modification status of a protein/peptide by gel analysis.

However, Clauser et al. disclose a method involving mass spectrometry and two-dimensional polyacrylamide gel electrophoresis for the rapid identification and characterization of proteins. The method can detect and structurally characterize covalent modifications. The authors have characterized several post-translational modification and chemical modifications that may result from electrophoresis or subsequent sampling processing steps. The detection of these modifications is required in order to reliably and unambiguously establish the identify of each protein. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure post-translational protein modification as taught by Clauser et al. in the method of Aebersold et al. (WO 00/11208) in view of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807) because Clauser et al. taught that the method allowed for the study cell-type dependent gene expression and large suites of cellular proteins with unprecedented speed and rigor. See abstract and page 5076.

IV. Claims 1-8 and 10-21 are rejected 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999).

Aebersold et al. teach methods of analyzing proteins or protein function in complex mixtures. The method utilizes a labeling compositions comprising the formula A-L-PRG. Wherein A represents an affinity label, PRG is a protein reactive group, and L is a linker group. This same formula is taught in the instant disclosure on page 8. The PRG selectively reacts with certain groups that are typically found in peptides (sulfhydryl, amino, carboxy, homoserine lactone groups). One or more affinity labeled reagents with different PRG groups is introduced into a mixture containing proteins. After protein A-L-PRG mixing the digestion is optional. The PRG complex binds with the proteins of interest to produce a measurable tagged binding entity. This entity can subsequently be evaluated/analyzed via liquid chromatography/mass spectrometry (LC/MS). See abstract and page 8.

The method can be employed to screen and identify proteins, which are differential expressed in cells, tissue, or biological fluids. It is further possible to determine the absolute amount of the proteins utilizing known amounts of internal standards. See page 9 1st paragraph. The process is applicable in determining the state of protein modification, enzyme activity, and function. See pages 9-11.

Aebersold et al. differ from the instant invention in not specifically including a protein separation step involving gel electrophoresis in their method.

However, Gygi et al. disclose methods for quantitative protein analysis. The method combines protein separation (two dimensional polyacrylamide gel electrophoresis-2D-PAGE) with mass spectrometry (MS) or tandem mass spectrometry (MS/MS). See page 994, 1st column, 2nd paragraph and page 998 2nd column last paragraph.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize electrophoresis separation along with MS or MS/MS as taught by Gygi et al. to identify the protein and or protein fragments found in the method of Aebersold et al., because Gygi et al. taught that their method allowed for large scale analysis of not only highly abundant proteins in cell lysates but could detect very-low abundance proteins as well. See page 998, 2nd column last paragraph.

Therefore one of ordinary skill in the art would have been motivated to include protein separation via electrophoresis and the mass spectrometry analysis procedure in order to acquire rapid and precise evaluation of all proteins (high and low) within a sample.

V. Claim 9 is rejected 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) and in further of Bienvenut et al. (Analytical Chemistry, 1999, 71, 4800-4807).

Please see Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) as set forth above.

Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) differ from the instant invention in failing to teach transblotting and digestion combinations in protein identification.

Bienvenut et al. disclose methods of combining transblotting (OSDT) and in gel digestion of all proteins in parallel (PIGD) to increase the throughput of protein identification and characterization in proteome studies. Peptides liberated during transblotting of proteins through an immobilized trypsin membrane were trapped on a PVDF membrane and identified by mass spectrometry. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the OSDT/PIG combination procedure of Bienvenut et al. in the protein identification method of Aebersold et al. in view of Gygi et al., because Bienvenut et al. taught that the combination "led to greatly improved digestion of high molecular weight and basic proteins without loss of low molecular weight polypeptides. See abstract.

One of ordinary skill in the art would have been motivated to employ the combination procedure of Bienvenut et al. to take advantageous of an automated integrated system involving MALDI-TOF MS scanning, spectra treatment, protein identification, in order to generate a fully annotated 2-DE map. See page 4807.

VI. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) and in further view of Clauser et al. (Proceedings of the National Academy of Sciences, USA, 1995, 92(11), 5072-6).

See Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) as set forth above.

Aebersold et al. in view of Gygi et al. differ from the instant invention in not specifically teaching post-translational modification status of a protein/peptide by gel analysis.

However, Clauser et al. disclose a method involving mass spectrometry and two-dimensional polyacrylamide gel electrophoresis for the rapid identification and characterization of proteins. The method can detect and structurally characterize covalent modifications. The authors have characterized several post-translational modification and chemical modifications that may result from electrophoresis or subsequent sampling processing steps. The detection of these modifications is required in order to reliably and unambiguously establish the identify of each protein. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to measure post-translational protein modification as taught by Clauser et al. in the method of Aebersold et al. (WO 00/11208) in view of Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) because Clauser et al. taught that the method allowed for the study cell-type dependent gene expression and large suites of cellular proteins with unprecedented speed and rigor. See abstract and page 5076.

***Response to Arguments***

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to the argument that Aebersold's do not teach a method wherein the labeled protein is separated first (such as affinity, electrophoresis, etc) and then subjected to proteolytic digestion. This argument was carefully considered but not found persuasive because Aebersold et al. are cited in combination with Bienvenut et al. and Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999). Bienvenut et al. disclose procedures of protein sample separation prior to digestion. For example see page 4802. Gygi et al. (Nature Biotechnology, Vol.17, 10/99, pages 994-999) disclose protein separation.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., separation prior to digestion) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims merely read on a digestion in claim 1 step (f), however there is no indication as to when the digestion takes place.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Applicant contends that there is not motivation to modify Aebersold et al. to include electrophoresis separation and digestion as taught by Bienvenut et al. and Gygi et al. This argument was carefully considered but not found persuasive because all the cited references to Aebersold et al., Bienvenut et al., and Gygi et al. are drawn to proteome studies. See Aebersold et al. - page 2 and Bienvenut et al. – abstract and Gygi et al. – page 994 2nd column 2nd paragraph. Further protein separation and protein digestion modifications and/or combinations were taught to be routinely adjusted in order to improve proteome procedures. See Bienvenut et al. page 4804 2nd column 2nd and 3rd paragraphs.

In response to applicant's argument that the separation of protein mixtures prior to digestion eliminates interfering materials, it is noted that the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant's arguments regarding the combination of Aebersold et al. in view of Sechi et al. as inoperable were carefully considered and found persuasive. Accordingly the reference to Sechi et al. has been withdrawn from the rejections rendering the arguments MOOT.

Applicant's arguments with respect to the dependent claims were directed to the combination of Aebersold et al. in view of Sechi et al., the rejection has been withdrawn and all the other arguments have been addressed.

7. For reasons aforementioned, no claims are allowed.

8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 872-9306, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to Group 1600, whose telephone number is (571) 272-1600.

Lisa V. Cook
Remsen 3C-059
(571) 272-0816
2/26/04

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
03/05/04